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The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia:

Integration of resting EEG, fMRI, and volumetric techniques

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Abstract

Anhedonia, the reduced propensity to experience pleasure, is a promising endophenotype and vulnerability factor for several psychiatric disorders, including depression and schizophrenia. In the present study, we used resting electroencephalograms, functional magnetic resonance imaging, and volumetric analyses to probe putative associations between anhedonia and individual differences in key nodes of the brain's reward system in a non-clinical sample. We found that anhedonia, but not other symptoms of depression or anxiety, was correlated with reduced nucleus accumbens (NAcc) responses to rewards (gains in a monetary incentive delay task), reduced NAcc volume, and increased resting delta current density (i.e., decreased resting activity) in the rostral anterior cingulate cortex (rACC), an area previously implicated in positive subjective experience. In addition, NAcc reward responses were inversely associated with rACC resting delta activity, supporting the hypothesis that delta might be lawfully related to activity within the brain's reward circuit. Taken together, these results help elucidate the neural basis of anhedonia and strengthen the argument for anhedonia as an endophenotype for depression.

Keywords: depression; anhedonia; striatum; reward; anterior cingulate cortex

Introduction

Early theorists suggested that anhedonia, the reduced propensity to experience pleasure, might constitute a vulnerability factor for psychiatric disorders, including Major Depressive Disorder (MDD) and schizophrenia (e.g., Meehl, 1975; Rado, 1956). Consistent with this view, anhedonia is currently considered a promising endophenotype of MDD, because it is a cardinal symptom of the disorder but is considerably more homogeneous, more easily quantified, and tied to dysfunction in the neural circuitry of reward, which is increasingly well-understood (Hasler et al., 2004; Pizzagalli et al., 2005). Therefore, information on the neural correlates of anhedonia may provide valuable insights into the pathophysiology and etiology of psychiatric disorders and may ultimately allow for early identification of high-risk individuals.

The neural systems underlying reward and pleasure have long been the object of scientific scrutiny (for a recent review, see Berridge and Kringelbach, 2008). Starting from early self-stimulation studies in rodents performed by Olds and Milner (1954), a large body of animal work has emphasized the role of mesocorticolimbic pathways in incentive motivation and the experience of pleasure. Even before the advent of modern neuroimaging techniques, Heath (1972) demonstrated that activation of these areas has powerful, positive motivational effects in humans by documenting fervent self-stimulation in a patient implanted with electrodes into the dopamine-rich mesolimbic septum/nucleus accumbens (NAcc) region. More recently, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have described increased activation in the basal ganglia, including the ventral striatum, in response to various appetitive cues (see Phan et al., 2002, for a review). Furthermore, PET studies using dopaminergic tracers have shown that the positive subjective effects of amphetamine are correlated with receptor binding in the ventral striatum (e.g., Drevets et al., 2001; Leyton et al., 2002; Oswald et al., 2005). Thus, the role of

the ventral striatum in reward processing has been firmly established using multiple methods.

Neuroimaging studies have also linked the experience of pleasure to neural activity in the medial prefrontal cortex (Berridge and Kringelbach, 2008; Phan et al., 2002). In particular, Rolls and colleagues (de Araujo et al., 2003; Grabenhorst et al., 2008; Rolls et al., 2003, 2008) have described an association between subjective ratings of pleasantness for a wide variety of stimuli from different modalities and responses to these stimuli in ventromedial prefrontal cortex (vmPFC) and rostral anterior cingulate cortex (rACC) regions (Figure 1). These cortical areas receive dense dopaminergic inputs (Gaspar et al., 1989), project to the striatum (in particular the NAcc) and the ventral tegmental area (Haber et al., 2006; Öngür and Price, 2000; Sesack and Pickel, 1992), show activity increases in response to dopamine-inducing drugs (Udo de Haes et al., 2007; Völlm et al., 2004), and have been implicated in preference judgments (e.g., Paulus and Frank, 2003), consistent with a role in reward-guided decision making (Rushworth et al., 2007).

Complementing these findings, emerging evidence from neuroimaging studies in clinical samples indicates that anhedonic symptoms are linked to reward responses in key nodes of the reward system (Epstein et al., 2006; Juckel et al., 2006a, 2006b; Keedwell et al., 2005; Mitterschiffthaler et al., 2003; Tremblay et al., 2005). For example, Epstein et al. (2006) reported that depressed subjects were characterized by reduced ventral striatal responses to positive pictures, and the strength of these responses was negatively correlated with self-reported anhedonia. Similarly, in a sample of twelve patients with MDD, Keedwell et al. (2005) found a negative correlation between anhedonia (but not depression severity) and ventral striatal responses to positive stimuli. Interestingly, these authors also found a *positive* correlation between anhedonia and responses in the vmPFC (BA10) and rACC (BA24/32). In what seems to be the only neuroimaging study on the brain correlates of anhedonia in healthy subjects, Harvey et al. (2007) did not observe a significant correlation

between anhedonia and ventral striatal responses to positive pictures. They did, however, replicate Keedwell et al.'s (2005) observation of a *positive* correlation between anhedonia and responses to positive stimuli in a region in the vmPFC, again extending into the rACC. In addition, Harvey et al. (2007) found that anhedonia was associated with reduced volume in caudate regions extending into the NAcc.

Taken together, these previous findings suggest that anhedonia may be associated with weaker responses to positive stimuli and reduced volume in the striatum, as well as with increased responses to positive stimuli in vmPFC/rACC. The latter association is surprising, given that activity in vmPFC/rACC is also positively related to ratings of pleasure as detailed above (e.g., de Araujo et al., 2003; Grabenhorst et al., 2008; Rolls et al., 2008; Rolls et al., 2003). Importantly, the vmPFC/rACC figures prominently in the brain's default network, which is activated during resting, task-free states and becomes deactivated when participants engage in a task (Buckner et al., 2008). Indeed, converging lines of evidence raise the possibility that associations between anhedonia and task-related activation in medial frontal regions may reflect individual differences in resting state activity.

First, depression has been associated with dysfunctional resting activity in vmPFC/rACC, with some studies reporting decreased (e.g., Drevets et al., 1997; Ito et al., 1996; Mayberg et al., 1994) and others increased (e.g., Kennedy et al., 2001; Videbech et al., 2002) activity, and decreased resting rACC activity has been found to predict a poor response to treatment (Mayberg et al., 1997; Mülert et al., 2007; Pizzagalli et al., 2001). Second, using both PET and measurements of electroencephalographic (EEG) activity, Pizzagalli et al. (2004) reported decreased resting activity (i.e., reduced glucose metabolism and increased delta activity) in the subgenual ACC (BA 25) in patients with melancholia – a depressive subtype characterized by psychomotor disturbances and pervasive anhedonia. Finally, various conditions and diseases characterized by reduced resting medial PFC activity are associated

with reduced task-induced medial PFC deactivation (Fletcher et al., 1998; Kennedy et al., 2006; Lustig et al., 2003), and recent findings by Grimm et al. (2008) indicate that this may also apply to depression. Specifically, these authors observed smaller task-induced deactivations in depressed individuals versus controls in several areas of the default network, including an area closely matching the ones implicated by Keedwell et al. (2005) and Harvey et al. (2007). Collectively, these observations suggest that the seemingly paradoxical positive association between anhedonia and vmPFC/rACC activation to positive stimuli might be due to an association between reduced baseline activity in this area and anhedonia, resulting in smaller deactivations during stimulus-processing. To our knowledge the hypothesis of an association between lower resting vmPFC/rACC activity and anhedonia has not been tested previously.

If such an association exists, it is likely to be evident in the delta frequency band of the EEG. As Knyazev (2007) recently noted in his review of the functional roles of different EEG oscillations, a number of observations support the idea that the delta rhythm is a signature of reward processing and salience detection. First, animal studies have identified generators of delta activity in key nodes of the brain reward system, such as the NAcc (Leung and Yim, 1993), ventral pallidum (Lavin and Grace, 1996), and dopaminergic neurons of the ventral tegmental area (Grace, 1995). Second, although electrical activity in the striatum cannot be measured noninvasively in humans, EEG source localization studies have implicated anterior medial frontal regions in the generation of delta activity (Michel et al., 1992; 1993). Critically, these sources overlap with regions reciprocally connected to the ventral tegmental area and emerging from fMRI studies as being associated with self-reported pleasure responses (see above). Third, the available animal data suggest that dopamine release in the NAcc is associated with decreased delta activity (Chang et al., 1995; Ferger et al., 1994; Kropf and Kuschinsky, 1993; Leung and Yim, 1993; Luoh et al., 1994). Fourth,

opioid and cocaine administration have been associated with changes in delta activity in humans (Greenwald and Roehrs, 2005; Reid et al., 2006; Scott et al., 1991). However, in contrast to the animal data, increases instead of decreases in delta activity were observed (see also Heath, 1972). Whereas these apparent discrepancies between animal and human data currently cannot be resolved, the available evidence nonetheless suggests that EEG delta activity may be linked to reward processing. Therefore the present study aims to further elucidate the proposed link between delta and reward.

In sum, the major goals of the present investigation were: (1) to examine whether anhedonia is negatively and positively associated with reward response in the ventral striatum and the vmPFC/rACC, respectively, as assessed by fMRI in conjunction with a monetary incentive delay task known to recruit the brain's reward network (Dillon et al., 2008); (2) to replicate Harvey et al.'s (2007) observation of an inverse association between anhedonia and striatal volume; (3) to investigate whether anhedonia is associated with increased resting EEG delta current density (i.e., decreased resting activity) in vmPFC/rACC; and (4) to probe the suggested link between EEG delta activity and the brain's reward system (Knyazev, 2007) by assessing the correlation between striatal reward responses measured via fMRI and resting EEG delta current density in the vmPFC/rACC.

Materials and methods

Participants

Data from the present report stem from a larger study that integrates behavioral, electrophysiological (resting EEG, event-related potentials), and neuroimaging (fMRI, structural MRI) measures as well as molecular genetics to investigate the neurobiology of reward processing and anhedonia in a non-clinical sample. A previous publication on this sample has focused on event-related potential data collected during a reinforcement task (Santesso et al., 2008), and a report on links between candidate genes and the fMRI data is in

preparation (Dillon, Bogdan, Fagerness, Holmes, Perlis, and Pizzagalli, in preparation).

Unlike prior reports, the primary goal of the current study was to investigate relations between individual differences in anhedonia and (1) resting EEG data, and (2) functional and volumetric measurements of reward-related basal ganglia regions. Secondary analyses aimed to evaluate interrelations among the three neuroimaging modalities.

In an initial behavioral session, 237 healthy adults between 18 and 40 years old completed a two-alternative forced choice task in which correct identification of one of two stimuli was rewarded more frequently. Prior work in independent clinical and non-clinical samples revealed that this probabilistic reward task is sensitive to variation in reward responsiveness and anhedonia (Bogdan and Pizzagalli, 2006; Pizzagalli et al., 2009; Pizzagalli et al., 2005). Based on their performance in the initial session, 47 of the 170 subjects meeting inclusion criteria for the current study (right-handedness; absence of medical or neurological illnesses, pregnancy, current alcohol/substance abuse, smoking, use of psychotropic medications during the last 2 weeks, or claustrophobia) were invited for the EEG and fMRI sessions (session order counterbalanced). Participants were selected to cover a wide range of individual differences in reward learning as measured by the probabilistic reward task: specifically, we first identified participants in the upper and lower 20% of the distribution of reward learning, and then selected remaining participants with the goal of achieving a continuum in reward learning that would be representative of the general population (for further details on the selection criteria, see Santesso et al., 2008).

Of these 47 participants, 41 (5 African American, 5 Asian, 29 Caucasian, 2 other) agreed to participate in the EEG session, and 33 of these also completed the fMRI session. All 41 participants (mean age: 21.2 years, S.D.: 3.1; mean education: 14.2 years, S.D.: 1.5; 20 male) had usable resting EEG data. Of the 33 participants who completed both sessions, five were excluded from the fMRI analyses due to excessive motion artifacts resulting in a sample

of $N = 28$ for the fMRI analyses (mean age: 21.5 years, S.D.: 3.5; mean education: 14.5 years, S.D.: 1.6; 14 male). Apart from one participant with specific phobia and one with minor depressive disorder, none of the participants had current psychiatric disorders, as determined with the Structured Clinical Interview for DSM-IV. There was evidence of past Axis I pathology in a minority of participants (past MDD: $n = 1$; past depressive disorder not otherwise specified: $n = 1$; past binge eating disorder: $n = 1$; past anorexia nervosa: $n = 1$; past alcohol abuse: $n = 1$).

Participants received approximately \$12, \$45, and \$80 for the behavioral, EEG, and fMRI sessions, respectively, in task earnings and reimbursement for their time. All participants provided written informed consent and all procedures were approved by the Committee on the Use of Human Subjects at Harvard University and the Partners-Massachusetts General Hospital Internal Review Board.

Procedure

Behavioral session. At both the behavioral and EEG session, the short version of the Mood and Anxiety Symptom Questionnaire (MASQ, Watson et al., 1995) was administered to measure depression-specific symptoms (Anhedonic Depression, AD), anxiety-specific symptoms (Anxious Arousal, AA) and general distress symptoms common to both depression and anxiety (General Distress: Depressive Symptoms, GDD; General Distress: Anxious Symptoms, GDA). Prior studies indicate that all MASQ scales possess excellent reliability (coefficient alpha: .85-.93 in adult and student samples) and convergent/discriminant validity with regard to other anxiety and depression scales (e.g., Watson et al., 1995). In the current sample, the test-retest reliability between the behavioral and EEG session (average interval = 36.6 days; range 2-106 days) of the AD, GDD, AA, and GDA scales was .69, .62, .49, and .70, respectively, indicating moderate to high stability. In the present analyses we only analyzed the MASQ scores from the behavioral session in order to (1) demonstrate the

predictive validity of the self-report measures for the physiological measures, and (2) minimize the influence of state effects on the MASQ-physiology correlations by ensuring that both EEG and fMRI measures were obtained at a different session from the MASQ data. However, very similar results emerged when analyzing the averages of the two MASQ administrations (data available upon request). In addition, the state version of the Positive and Negative Affect Schedule (PANAS, Watson et al., 1988) was administered at both the behavioral and the EEG sessions to assess current mood.

Resting EEG session. Participants were instructed to sit still and relax while the resting EEG was recorded for eight minutes (4 minutes with eyes open, 4 minutes with eyes closed in counterbalanced order). Subsequently, participants repeated the probabilistic reward task used for subject selection during event-related potential recordings (Santesso et al., 2008).

MRI session. After collection of structural MRI data, participants performed a monetary incentive delay (MID) task during functional imaging. The MID has been described earlier in an independent sample (Dillon et al., 2008). Briefly, participants completed 5 blocks of 24 trials. Each trial began with the presentation of one of three equally probable cues (duration: 1.5 s) that signaled potential monetary gains (+\$), no incentive (0\$), or losses (-\$). After a jittered inter-stimulus interval (ISI) of 3-7.5 s, a red square was presented to which participants responded with a button press. Following a second jittered ISI (4.4-8.9 s), feedback was presented indicating a gain (range: \$1.96 to \$2.34; mean: \$2.15), no-change, or penalty (range: -\$1.81 to \$2.19; mean -\$2.00). Participants were told that their reaction time (RT) to the target affected trial outcomes such that rapid RTs increased the probability of receiving gains and decreased the probability of receiving penalties. In fact, 50% of reward and loss trials resulted in delivery of gains and penalties, respectively (see Dillon et al., 2008, for further detail). Outcome delivery was de-coupled from responses in this fashion in order

to permit a fully balanced design, with an equal number of trials featuring each outcome. However, to maintain task believability and engagement, for trials leading to a positive outcome (e.g., gains in reward trials), target exposure time corresponded to the 85th percentile of RTs collected during a 40-trial practice session administered immediately before scanning; for trials scheduled to yield a negative outcome (e.g., no gains in reward trials), target exposure time corresponded to the 15th percentile of practice RTs. The order of outcome delivery was based on a pre-determined sequence that optimized the statistical efficiency of the fMRI design (Dale, 1999).

Data Collection and Analyses

EEG recording. Resting EEG was recorded using a 128-channel Electrical Geodesic system (EGI Inc., Eugene, OR) at 250 Hz with 0.1-100 Hz analog filtering referenced to the vertex. Impedances were kept below 50 k Ω . Data were re-referenced off-line to an average reference. After correcting eye-movement artifacts using an Independent Component Analysis implemented in Brain Vision Analyzer (Brain Products GmbH, Germany), the data were visually scored for remaining artifacts, and corrupted channels were interpolated using a spline interpolation.

Following prior procedures (e.g., Pizzagalli et al., 2001, 2004, 2006), Low Resolution Electromagnetic Tomography (LORETA, Pascual-Marqui et al., 1999) was used to estimate resting intracerebral current density in various frequency bands. To this end, spectral analyses were first performed on artifact-free 2048-ms epochs using a discrete Fourier transform and boxcar windowing. LORETA was then used to estimate the intracerebral current density distribution for the following bands: delta (1.5-6.0 Hz), theta (6.5-8.0 Hz), alpha1 (8.5-10.0 Hz), alpha2 (10.5-12.0 Hz), beta1 (12.5-18.0 Hz), beta2 (18.5-21.0 Hz), beta3 (21.5-30.0 Hz), and gamma (36.5-44.0 Hz). Based on prior findings (e.g., Knyazev, 2007; Pizzagalli et al.,

2004; Scheeringa et al., 2008), delta activity was the main frequency of interest; other EEG bands were analyzed to evaluate the specificity of possible findings.

At each voxel ($n = 2394$; voxel resolution = 7 mm³), current density was computed as the squared magnitude of the intracerebral current density within each of the eight frequency bands (unit: amperes per square meter, A/m²). For each subject and band, LORETA values were normalized to a total power of 1 and then log transformed before statistical analyses. Voxel-by-voxel Pearson correlations between MASQ AD and log-transformed delta current density were then computed and displayed on a standard MRI template (MNI space) after thresholding at $p < .001$ (uncorrected).

In addition to voxel-by-voxel correlations, we also analyzed current density in several *a priori* defined regions of interest (ROIs) within the ACC. This approach was selected to (1) increase statistical power, (2) allow comparisons between MASQ AD and the other MASQ scales unbiased by statistical thresholding (i.e., evaluation of symptom-specificity), and (3) allow comparisons among various ACC subdivisions (i.e., evaluation of region-specificity). To this end, for each subject and band, average current density was computed for the following subdivisions of the ACC (for details see Bush et al., 2000; Pizzagalli et al., 2006): the more rostral, “affective” subregions, including BA25 (17 voxels, 5.83 cm³), BA24 (12 voxels, 4.12 cm³), and BA32 (17 voxels, 5.83 cm³), and the more dorsal, “cognitive” subregions, including BA32' (20 voxels, 6.86 cm³) and BA24' (48 voxels, 16.46 cm³). Location and extent of these subdivisions were defined based on Structure-Probability Maps (Lancaster et al., 1997) and anatomical landmarks (Devinsky et al., 1995; Vogt et al., 1995), as previously described in detail (Pizzagalli et al., 2006). On average, estimates of resting current density were based on 110.7 artifact-free epochs (S.D.: 37.2, range: 37-174). Log-transformed delta current density in BAs 24, 25, and BA32 was not associated with either the

total number of artifact-free epochs or the percentage of eyes-open epochs contributing to the individual averages, all $r_s(39) \leq .10$, $p \geq .52$.

fMRI data. The imaging protocol and fMRI processing stream have been described previously (Dillon et al., 2008; Santesso et al., 2008). Briefly, fMRI data were acquired on a 1.5 T Symphony/Sonata scanner (Siemens Medical Systems; Iselin, NJ). During functional imaging, gradient echo T2*-weighted echoplanar images were acquired using the following parameters: TR/TE: 2500/35; FOV: 200 mm; matrix: 64 x 64; 35 slices; 222 volumes; voxels: 3.125 x 3.125 x 3 mm. A high-resolution T1-weighted MPRAGE structural volume was collected for anatomical localization and extraction of structural ROIs using standard parameters (TR/TE: 2730/ 3.39 ms; FOV: 256 mm; matrix: 192 x 192; 128 slices; voxels: 1.33 x 1.33 x 1 mm). Padding was used to minimize head movement.

Analyses were conducted using FS-FAST (<http://surfer.nmr.mgh.harvard.edu>) and FreeSurfer (Fischl et al., 2002; Fischl et al., 2004). Pre-processing included motion and slice-time correction, removal of slow linear trends, intensity normalization, and spatial smoothing with a 6 mm FWHM Gaussian filter. A temporal whitening filter was used to estimate and correct for autocorrelation in the noise. Next, a gamma function (intended to model the hemodynamic response) was convolved with stimulus onsets, and the general linear model assessed the fit between the model and the data. Participants with incremental (volume-to-volume) or cumulative head movements greater than 3.75 mm or degrees were removed from the analysis ($n = 5$). For the remaining participants, motion parameters were included in the model as nuisance regressors.

For this study, the main fMRI results of interest were regression coefficients (beta weights) extracted from four components of the basal ganglia (NAcc, caudate, putamen, and globus pallidus) and the rACC.¹ These ROIs were structurally defined by FreeSurfer's automatic cortical and sub-cortical parcellation algorithms, which are highly reliable and

compare favorably to manual methods (Desikan et al., 2006; Fischl et al., 2002; Fischl et al., 2004). For each participant and ROI, mean beta weights were extracted for delivery of monetary gains, monetary penalties, and no-change feedback. For the sake of consistency with prior neuroimaging work, in which anhedonia has been associated with brain activation to actual positive stimuli (Epstein et al., 2006; Harvey et al., 2007; Keedwell et al., 2005), fMRI analyses focused on responses to outcomes. At the request of an anonymous reviewer, mean beta weights were also extracted for reward cues to evaluate the specificity of correlations with anhedonia vis-à-vis consummatory versus anticipatory phases of reward processing.

FreeSurfer's algorithms also provide volumetric information for each ROI and the total intracranial volume. To adjust for gender and intracranial volume, we *z*-standardized intracranial volume and the volumes of each of the ROIs within genders and then regressed the *z*-scores for each ROI on the *z*-scores for intracranial volume. This regression approach was selected to avoid introducing sex differences due to the larger intracranial volume in males relative to females. All statistical analyses for the volumetric variables were conducted with the residuals derived from these regressions.

Statistical Analyses

fMRI data were analyzed with mixed ANOVAs using *Feedback* (gain, no-change, penalty) and *Gender* (male, female) as factors. For basal ganglia regions, *Hemisphere* (left, right) and *Region* (NAcc, caudate, putamen, pallidus) were added as additional within-subject factors. The Greenhouse-Geisser correction was used when applicable. Pearson correlations and partial correlations were computed to test the main hypotheses. Differences between dependent correlation coefficients were tested using the formula proposed by Steiger (1980). Results are reported with an alpha-level of 0.05 (two-tailed) unless otherwise noted. In light

of prior findings (Epstein et al., 2006; Harvey et al., 2007), the *a priori* hypotheses of negative correlations between anhedonia and (1) NAcc volume and (2) NAcc response to rewards were tested one-tailed. Primary analyses involved five predicted correlations (anhedonia–NAcc volume, anhedonia–NAcc response to gains, anhedonia–rACC response to gains, anhedonia–resting rACC delta activity, NAcc response to gains–resting rACC delta activity). All other correlations were performed in order to test the specificity of the five main findings; consequently, corrections for multiple testing were not implemented.

Results

Intercorrelations of MASQ and PANAS Scales

As shown in Table 1, the MASQ scales were moderately to highly correlated with each other and with PANAS state negative affect in both sessions. However, mirroring prior observations (Watson and Clark, 1995), only MASQ AD displayed a significant negative correlation with PANAS state positive affect at both sessions. Mean and standard deviation of MASQ AD (weighted by gender) did not differ from the values reported by Watson et al. (1995, Table 1) for a large student sample, $t(1112) = 1.28, p = .20, F(40, 1072) = 1.07, p = .35$.

Basal Ganglia and rACC Responses to Monetary Gains and Penalties

To verify that the basal ganglia were activated by monetary gains in the MID task, we computed a *Feedback* x *Region* x *Hemisphere* x *Gender* ANOVA. Findings revealed a significant main effect of *Feedback*, $F(2, 51.5) = 8.00, p = .001$, and a significant *Feedback* x *Region* interaction, $F(3.3, 85.6) = 6.97, p = .0003$ (see Figure 2 A). *A priori* specified contrasts revealed that all basal ganglia regions were activated more strongly by gains versus no-change feedback, $F(1, 26) \geq 4.43, p \leq .045$. Notably, only the NAcc was associated with

reduced activity after penalties relative to no-change feedback, $F(1, 26) = 3.83, p = .06$. Thus, across hemispheres and gender, the basal ganglia was reliably activated by gains, and only the NAcc showed signs of deactivation after penalties relative to no-change feedback.

To evaluate whether the structurally defined rACC ROI was activated by monetary gains, we computed a *Feedback* x *Gender* ANOVA and obtained a significant main effect of *Feedback*, $F(1.9, 50.4) = 5.63, p < .007$ (Figure 2 B). *A priori* specified contrasts revealed higher activation to gains versus no-change feedback, $F(1, 26) = 12.48, p = .002$, as well as higher activation to penalties versus no-change feedback, $F(1, 26) = 4.18, p = .051$.

Functional and Structural Correlates of Anhedonia

Relationship with NAcc responses to gains and penalties. As hypothesized, anhedonia as measured by the MASQ AD was negatively associated with NAcc responses to gains averaged across the two hemispheres, $r(26) = -.43, p = .011$, one-tailed (see Table 2 and Figure 3A). No significant correlations were observed between MASQ AD and gain-related responses in any of the other four regions of interest (putamen, caudate, pallidus, rACC). Highlighting the specificity of these findings, none of the other MASQ scales correlated significantly with the NAcc responses to gains (see Table 2), and the correlation between MASQ AD and NAcc gain responses remained virtually unchanged after simultaneously partialling out the other three MASQ scales, $r(23) = -.35, p = .041$, one-tailed. Furthermore, the correlation between MASQ AD and NAcc responses to gains differed significantly from the (non-significant) correlations between MASQ AD and NAcc responses to penalties, $r(26) = .25, p = .20, z = 2.41, p = .016$, or no-change feedback, $r(26) = .11, p = .58, z = 2.30, p = .021$. Although not a main focus of the present study, NAcc responses to penalties were positively correlated with MASQ GDA scores (see Table 2), indicating that more anxious participants showed stronger NAcc responses to penalties.²

Supplementary analyses examining responses to reward cues did not reveal any significant correlations with MASQ AD for the NAcc, $r(26) = .12$, $p = .54$, or any of the other four ROIs, $|r(26)| \leq .25$, $p \geq .20$. In addition, the correlation between MASQ AD and NAcc responses to gains was significantly stronger than the correlation involving NAcc responses to reward cues, $z = 2.03$, $p = .04$, indicating that the association was specific to reward consumption rather than anticipation.

Relationship with NAcc volume. As shown in Table 2 and Figure 3B, MASQ AD displayed a negative correlation with NAcc volume (adjusted for gender and intracranial volume) that remained significant after simultaneously partialling out the other three MASQ scales, $r(23) = .38$, $p = .03$, one-tailed. No significant associations were observed between MASQ AD and the adjusted volumes of the other basal ganglia regions, $.22 \geq r(26) \geq .02$, $ps \geq .27$. Moreover, NAcc volume and NAcc reward responses to gains were uncorrelated (Table 2), indicating that both variables explained separate components of MASQ AD variance (see below).

Relationship with resting EEG delta current density. The computation of voxel-by-voxel correlations between MASQ AD and log-transformed delta current density identified only one cluster of positive correlations significant at $p < 0.001$. As shown in Figure 1, this functionally defined ROI (16 contiguous voxels, 5.49 cm^3) was located in rACC regions overlapping with areas emerging from fMRI studies of anhedonia and pleasure ratings. Furthermore, MASQ AD was positively correlated with resting delta current density in each of the three *a priori* defined affective subdivisions of the ACC (BAs 24, 25, and 32; see Figure 3C and Table 2).

Control analyses indicated that this finding was characterized by substantial specificity. First, the MASQ AD scores did not correlate with delta current density in the more dorsal, cognitive subdivisions of the ACC ($rs = .12$ and $.04$ for BA24' and BA32',

respectively), highlighting region-specificity. Second, all significant correlations between MASQ AD and delta current density shown in Table 2 remained significant after simultaneously partialling out the other three MASQ scales, $r(36) \geq .33, p \leq .042$, emphasizing symptom-specificity. In contrast, the correlations between MASQ GDD and delta current density in BA32 and the functionally defined ROI (see Table 2) were no longer significant after partialling out MASQ AD, $r(38) = .09$. In addition, the MASQ AD-delta current density correlations remained significant after simultaneously partialling out participants' ratings of state positive and negative affect during both the MASQ administration and EEG recording, $r(33) \geq .39, p \leq .021$, suggesting that the observed associations were not based on individual differences in affective state during the experimental sessions.³ Finally, as hypothesized, associations between MASQ AD scores and resting EEG activity were strongest for the delta band.⁴

Relationship Between Resting EEG Delta Current Density and NAcc Responses to Gains.

As shown in Table 2, NAcc responses to gains, but not penalties, were negatively correlated with delta current density both in the functionally defined ROI and in the *a priori* defined rACC subdivisions, $rs(26) \leq -.41, ps \leq .031$. Furthermore, these correlations differed ($1.60 \leq z \leq 2.62, p \leq .11$) from analogous correlations with NAcc responses either to penalties, $rs(26) \leq .16, ps \geq .42$, or no incentive feedback, $rs(26) \leq .07, ps \geq .71$. Emphasizing the specificity of the association between resting delta activity in the rACC and NAcc responses to gains, no correlations emerged between delta current density in the rACC and either responses to gains in any of the other basal ganglia regions or responses to reward cues in the NAcc.

Controls for potential influences of gender and outliers

All significant correlations in Table 2 remained at least marginally significant ($p \leq .05$, one-tailed), when all variables were first standardized within gender and Spearman's rank correlations instead of Pearson's correlations were computed. Thus, neither gender differences nor outliers were driving the associations. In addition, none of the significant associations in Table 2 were significantly moderated by gender, indicating that similar correlations were observed for men and women.

Multivariate Model Predicting Anhedonia

To evaluate unique and cumulative contributions of the various physiological variables to anhedonia, NAcc responses to gains, NAcc volume, and resting delta current density in the rACC (functional ROI) were simultaneously entered in a multiple regression predicting MASQ scores. Findings revealed that all three variables were significant predictors of anhedonia (NAcc responses to gains: $\beta = .30$, $p = .05$, one-tailed; NAcc volume: $\beta = -.43$, $p = .005$, one-tailed; resting delta rACC current density: $\beta = .37$, $p = .024$, two-tailed). Accordingly, components of MASQ AD variance explained by the three variables were at least partially independent, despite the significant association between the two measures of functional activity. Notably, the model explained 45% of the variance in anhedonic symptoms, $R^2 = .45$, $F(3, 24) = 6.44$, $p = .002$.

Discussion

This study integrated resting EEG, structural MRI, and fMRI to identify neural correlates of anhedonia, an important endophenotype and vulnerability factor for psychiatric disorders (e.g., Gooding et al., 2005; Hasler et al., 2004; Loas, 1996; Pizzagalli et al., 2005). As hypothesized, we observed (1) a negative association between anhedonia and NAcc responses to reward feedback (i.e., monetary gains), (2) a negative association between

anhedonia and NAcc volume, and (3) a positive association between anhedonia and resting EEG delta activity (i.e., low resting activity) in rACC. Contrary to our hypotheses, no correlations between rACC activation to reward feedback and anhedonia emerged. However, resting rACC delta activity was negatively associated with NAcc responses to gains, indicating that the delta rhythm is indeed associated with stimulus-elicited activity in the brain's reward circuit as suggested by Knyazev (2007). Thus, the present findings provide novel insights into both brain mechanisms associated with anhedonia and functional correlates of EEG delta activity.

Anhedonia and NAcc Structure and Function

Replicating prior work (Epstein et al., 2006; Keedwell et al., 2005), we found a negative correlation between anhedonic symptoms and NAcc responses to positive stimuli (monetary gains) measured at a separate session (on average, more than one month later). Unlike prior studies, the current analyses revealed that this association was specific to anhedonic symptoms (versus anxiety symptoms or general distress, as assessed by the three other MASQ scales), to the NAcc (versus the three other basal ganglia regions), to reward feedback (versus punishment and neutral feedback), and to the consumatory (versus anticipatory) phase of reward processing. These findings show that anhedonia predicts ventral striatal responses to rewarding stimuli not only in depressed patients (Epstein et al., 2006; Keedwell et al., 2005), but also in healthy subjects, and emphasize substantial specificity between reward-related NAcc responses and anhedonia. Providing initial insights into the causal direction underlying this association, Schlaepfer et al. (2008) recently showed that deep brain stimulation in the NAcc increased glucose metabolism in the stimulated region and alleviated anhedonia in three patients with treatment-resistant forms of depression. Taken together, these observations suggest that functional abnormalities in the NAcc play an

important role in the manifestation of anhedonia.

Replicating findings by Harvey et al. (2007), we also observed a specific negative association between MASQ AD (and not the other MASQ scales) and NAcc volume. In contrast to the prior study, this association was specific to NAcc and did not extend to other basal ganglia regions (e.g., caudate). Interestingly, the variance in anhedonia accounted for by structural differences in NAcc did not overlap with variance associated with individual differences in NAcc responses to gains. This raises the question whether the structural component represents variance in *trait* anhedonia, whereas the functional component may be largely based on individual differences in *state* anhedonia. At least two observations speak against this possibility. First, functional responses to incentives were assessed at a different session, which occurred, on average, more than a month after the MASQ administration. Thus, only mood states of considerable stability could underlie the observed associations. Second, we re-computed the correlations after averaging the MASQ AD scores across the behavioral and EEG sessions. These analyses revealed an increased correlation for NAcc responses to gains, $r(26) = -.49$, but not for NAcc volume, $r(26) = -.20$ (compare to values in Table 2). Consequently, it seems more likely that structural and functional differences in the NAcc tap into different aspects of neural reward processing that may nonetheless both be relevant to anhedonia.

In the current study, we are unable to pinpoint these separate aspects. In addition, further work will be needed to decompose the relative contributions of anticipatory versus consummatory aspects of reward processing to anhedonia. In animal work, hedonic “liking” has been associated with NAcc opioid activity, whereas NAcc dopamine appears to be more closely tied to incentive salience (“wanting”) and behavioral activation (Berridge, 2007; Salamone et al., 2007) and both “liking” and “wanting” might arguably be reduced in anhedonia. In our sample, the correlation between anhedonia and NAcc responses was

specific to the consummatory (“liking”) rather than anticipatory (“wanting”) phase of reward processing. This finding contrasts with recent data in schizophrenic patients, in which negative symptoms (including anhedonia) have been linked to ventral striatal responses to anticipatory cues in a similar version of the MID task (Juckel et al., 2006a, 2006b). In addition to clear differences in group composition (patients with schizophrenia vs. psychiatrically healthy subjects), differences in task design might explain the discrepancy between the current and Juckel’s findings. Specifically, unlike prior studies, in which 66% of reward trials led to reward feedback (Juckel et al., 2006a, 2006b), in the current study, gains were delivered on 50% of reward trials, and were thus more unpredictable. Because striatal responses have been found to be maximal when rewards are unpredictable (e.g., Delgado, 2007; O’Doherty et al., 2004), the current design might have increased our ability to identify lawful associations between NAcc responses to gains and anhedonia in this psychiatrically healthy sample. Based on these discrepancies, we believe it is premature to conclusively state whether anhedonia is primarily characterized by dysfunction in anticipatory vs. consummatory phases of reward processing. Future studies using a variety of experimental tasks and/or pharmacological manipulations of the dopamine and opioid systems will be needed to elucidate the roles of “wanting” and “liking” in anhedonia.

Anhedonia and rACC Function

In the present study, a positive association between anhedonia and resting EEG delta activity in rACC regions emerged. This association was specific to anhedonia (versus the other MASQ subscores), to rostral (versus dorsal, more cognitive) ACC subregions, and to the delta frequency band (with the exception of similar but weaker correlations in the theta band; see footnote 4). Furthermore, the cluster showing the strongest correlations between delta current density and anhedonia overlaps with regions where correlations between

anhedonia/depression and fMRI signal in response to pleasant stimuli have been found in prior work (e.g., Harvey et al., 2007; Keedwell et al., 2005). Given that resting delta oscillations are inversely correlated with resting brain activity across individuals (Niedermeyer, 1993; Pizzagalli et al., 2004; Reddy et al., 1992; Scheeringa et al., 2008), these observations support the hypothesis that anhedonia is associated with tonically decreased brain activity in an area of the brain that has been associated with subjective pleasure ratings in response to stimuli from various modalities (de Araujo et al., 2003; Grabenhorst et al., 2008; Rolls et al., 2008; Rolls et al., 2003). Moreover, it should also be noted that our observation of a positive correlation between anhedonia and delta current density in the subgenual ACC (BA25) emerging from the a priori ROI analyses nicely dovetails with prior findings of higher delta current density (and lower metabolic activity) in BA25 in depressive patients with melancholia (i.e., a subtype of major depression prominently characterized by anhedonia, Pizzagalli et al., 2004).

Taken together, the present findings (1) indicate that anhedonia, rather than general distress, anxiety or other traits and states typically elevated in depression, may be linked to altered brain functioning in rACC, and (2) suggest that anhedonia may not only be characterized by reduced NAcc responsivity to rewards, but also by tonically low resting activity in the rACC. The latter observation is novel but consistent with ample evidence that the rACC figures prominently in the brain's reward circuitry. It receives dense dopaminergic innervation (Gaspar et al., 1989) and projects to the striatum (in particular the NAcc) and the ventral tegmental area (Haber et al., 2006; Öngür and Price, 2000; Sesack and Pickel, 1992). In rats, stimulation of the rACC increases burst firing patterns in ventral tegmental area dopamine neurons (Gariano and Groves, 1988; Murase et al., 1993), and these burst firing patterns increase dopamine release in the NAcc (Schultz, 1998), which has been implicated in incentive salience and behavioral activation (see above). In humans, the rACC shows activity

increases in response to dopamine-inducing drugs (Udo de Haes et al., 2007; Völlm et al., 2004), reduced functional connectivity with striatal areas after dopamine depletion (Nagano-Saito et al., 2008), reduced reward-learning signals in treatment-resistant depression (Kumar et al., 2008), and has been implicated in subjective pleasure reactions (see above) and preference judgments (e.g., Paulus and Frank, 2003).

Critically, the rACC is also considered a key node of the brain's default network (i.e., a network of interconnected regions activated during resting states and deactivated during engaging tasks, Buckner et al., 2008), and Scheeringa et al. (2008) have demonstrated that frontal midline delta/theta activity is inversely correlated with activity in the default network. Thus, viewed from this perspective, the present findings suggest an association between anhedonia and reduced activity in the default network, which is thought to “facilitate flexible self-relevant mental explorations – simulations – that provide a means to anticipate and evaluate upcoming events before they happen” (Buckner et al., 2008, p. 2). Depressive patients underestimate the occurrence of positive stimuli presented to them (e.g., Pause et al., 2003) and anticipate fewer positive outcomes in the near future (MacLeod and Salaminiou, 2001; MacLeod et al., 1997; Miranda and Mennin, 2007; Moore et al., 2006). These observations raise the intriguing possibility that reduced resting activity in the rACC node of the default network may underlie difficulty with positive future-oriented mentation (i.e., underestimation of positive events in the past along with deficits in imagining positive scenarios for the future). Future studies will be needed to test this speculation.

Although the rACC was also reliably *activated* by reward feedback in the MID task, we did not observe the expected positive association between reward responses in this area and anhedonia (Harvey et al., 2007; Keedwell et al., 2005). We note, however, that positive associations between anhedonia/depression and rACC responses to positive stimuli have been reported most consistently in the context of overall rACC *deactivations* to emotional stimuli,

with healthy controls and individuals low in anhedonia showing the most pronounced deactivations (Gotlib et al., 2005; Grimm et al., 2008; Harvey et al., 2007). It is therefore possible that individuals with anhedonic symptoms do not display task-induced deactivations in this node of the brain's default network due to their abnormally low activity in this area under rest. This novel hypothesis, which might also explain the seemingly paradoxical positive associations between anhedonia and rACC reward responses observed in some studies (Harvey et al., 2007; Keedwell et al., 2005), could be readily tested in studies combining fMRI measures of task-related deactivation and PET or EEG measures of resting activity.

Rostral ACC Delta Activity and NAcc Reward Responses

The robust and specific negative correlations observed between delta current density in the more rostral, affective subdivisions of the ACC and the NAcc response to gains constitute novel evidence in healthy humans for the hypothesis that the EEG delta rhythm is associated with reward processing in the ventral striatum (Knyazev, 2007). The direction of this effect is consistent with animal data demonstrating that dopamine release in the NAcc is associated with decreased delta activity (Chang et al., 1995; Ferger et al., 1994; Kropf and Kuschinsky, 1993; Leung and Yim, 1993; Luoh et al., 1994) and with a recent report of increased event-related delta activity in pre-symptomatic Huntington's disease, a neurological disorder associated with marked reductions in striatal dopamine D1 and D2 receptor density (Beste et al., 2007). Specificity of the effect to rACC and NAcc constitutes further support for the hypothesized role for delta as an index of neural reward processing.

As described above, the rACC is itself an important node of the brain's reward circuitry and anatomical studies in monkeys have demonstrated that rACC regions preferentially project to the NAcc versus other striatal regions (Haber et al., 2006). Though

providing strong evidence for a link between delta and reward, the present findings from resting EEG data do not speak to the precise functions of delta activity in reward processing. Cohen, Elger, and Fell (2008) have recently reported that frontal midline delta activity decreases during anticipation of loss and win feedback and increases in response to the feedback itself, particularly to unexpected win feedback. These data suggest opposite changes in delta activity in the anticipatory and consummatory phases of reward processing and indicate how investigators could capitalize on the superior temporal resolution of the EEG to probe individual differences in the dynamics of neural reward processing.

Limitations and Conclusions

Apart from several strengths (e.g., use of multiple neuroimaging techniques, larger sample size than previous studies), we should also note some important limitations. First, because our sample primarily consisted of young undergraduates, it remains to be seen whether the present findings will generalize to other, more heterogeneous samples. Second, although we took several precautions to control for potential state influences on the observed association between anhedonia and the resting EEG (assessment at separate sessions, partialling of state affect), we cannot rule out that state affect contributed to the present findings. Studies with repeated assessments of resting EEG could provide interesting information on the relative importance of state and trait contributions to the variance in rACC delta activity (Hagemann et al., 2002). Third, studies with concurrent measurement of resting EEG and PET in sufficiently large samples are clearly warranted to bolster our interpretation of LORETA estimates of delta current density in the rACC as an inverse indicator of brain activity in this region, given that the coupling of (low) delta and regional glucose metabolism may not be as tight in clinical samples (Pizzagalli et al., 2004). Fourth, although the five correlations tested in the primary analyses were predicted *a priori* based on previous findings

and/or theoretical arguments, the current findings await replication due to the lack of correction for multiple comparisons. Finally, as with all correlational studies, the present findings do not imply causality, or even a causal direction. Accordingly, it is currently unknown whether reduced NAcc volume, for example, is a vulnerability factor for or a consequence of anhedonia. Future studies using longitudinal designs, experimental manipulations of striatal and medial PFC activity (e.g., Schlaepfer et al., 2008), and/or focusing on the molecular genetics of reward processing (e.g., Kirsch et al., 2006) will be needed to investigate more refined hypothesis about the neurobiological substrates of anhedonia.

Nonetheless, using a multi-modal neuroimaging approach, we showed that anhedonia is correlated with weaker NAcc responses to monetary gains, reduced NAcc volume, and increased resting EEG delta activity (i.e., reduced resting brain activity) in rACC regions in a sample of young volunteers. Collectively, these three physiological measures explained 45% of variance in anhedonic symptoms. Both anhedonia and the regions of the brain's reward system implicated in the present study have been linked to several severe psychiatric disorders, including depression and schizophrenia. Thus, our findings provide further support for the conceptualization of anhedonia as a promising endophenotype and vulnerability factor for these disorders, and suggest that further studies on the neural basis of anhedonia in healthy individuals may help overcome the limitations of the current psychiatric nosology and offer important insights into pathophysiology.

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Footnotes

¹ In an alternative analysis, we obtained average beta weights for spherical ROIs with an 8 mm radius centered on the approximate location of the peak correlation between anhedonia and the BOLD response to positive stimulation in the left and right ventromedial PFC ($x = \pm 8, y = 44, z = -7$) as reported by Harvey et al. (2007) and Keedwell et al. (2005). The results were very similar to those reported here for the rACC.

² Highlighting the specificity of this link, this correlation differed from the non-significant associations observed between MASQ GDA and NAcc responses to gains, $r(26) = -.19, p = .34, z = 2.07, p = .038$, and no-change feedback, $r(26) = -.00, p = .99, z = 1.71, p = .087$, and remained significant after simultaneously partialling the other three MASQ scales, $r(23) = .41, p = .041$. In spite of this promising specificity, the correlation between MASQ GDA and NAcc responses to monetary penalties should be interpreted cautiously, because it was not predicted and would not reach statistical significance after correction for multiple testing.

³ Two participants had missing data in at least one of their state positive and negative affect ratings and therefore could not be included in this analysis.

⁴ Similar but somewhat smaller correlations emerged between MASQ AD scores and theta current density, $rs(39) = .35, .30$, and $.45$, for BAs 24, 25, and 32, respectively, $p \leq .06$. Moreover, with the sole exception of a correlation between MASQ AD and beta1 current density in BA32, $r(39) = .33, p = .035$, no significant associations were observed between MASQ AD and current density in these areas in any of the other EEG frequency bands.

Figure Captions

Figure 1. LORETA whole-brain analyses. Results of voxel-by-voxel correlations between the Anhedonic Depression scale of the Mood and Anxiety Symptom Questionnaire (MASQ AD) and log-transformed delta (1.5-6.0 Hz) current density. The statistical map is thresholded at $p < .001$ (uncorrected). The red area indicates the only cluster with significant positive correlations. The slices displayed run through the voxel with the maximal correlation ($r = .534$, $N = 41$, $p = .0003$; MNI coordinates: 4, 38, 1). The circle and the triangles in the sagittal slice represent projections of peak activations from prior fMRI studies (x -coordinates for all peaks within ± 7). The yellow circle represents the area where two prior studies independently observed a significant positive correlation between anhedonia and the BOLD response to positive stimuli (Harvey et al., 2007; Keedwell et al., 2005). The triangles represent areas in which correlations between ratings of subjective pleasantness and the BOLD response to odors (green triangle, Rolls et al., 2003), tastes (light blue triangle, Grabenhorst et al., 2008), water in fluid-deprived subjects (dark blue triangle, de Araujo et al., 2003), as well as warm and cold stimuli applied to the hand (orange triangle, Rolls et al., 2008) have been described.

Figure 2. Mean beta weights (and standard errors) in (A) the four basal ganglia regions and (B) the rACC in response to monetary gains, no-change feedback, and monetary penalties (averaged across hemispheres). Note that only the nucleus accumbens (NAcc) showed a trend for smaller responses to penalties relative to no-change feedback.

Figure 3. Scatterplots for the correlations (A) between the Anhedonic Depression scale of the Mood and Anxiety Symptom Questionnaire (MASQ AD) and the NAcc response to monetary gains, (B) between MASQ AD and NAcc volume corrected for gender and intracranial

volume (see text for details), (**C**) between MASQ AD and log-transformed resting delta (1.5-6.0 Hz) current density in one of the *a priori* defined regions of interest in the rACC (BA32, see text for details), and (**D**) between NAcc response to monetary gains and log-transformed resting delta current density in BA32.

